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ORIGINAL ARTICLE

Analysis of Fulminant Cerebral Edema in Acute Pediatric Encephalitis

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Key Words
brain herniation;
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pediatric encephalitis;
status epilepticus

Background: Acute pediatric encephalitis with fulminant cerebral edema can rapidly become fatal or result in devastating neurological sequelae.
Methods: All cases coded with the discharge diagnosis of acute encephalitis between January 2000 and December 2010 were reviewed. Of the 1038 children with acute pediatric encephalitis, 25 were enrolled in our study with ages ranging from 5 months to 16 years.
Results: The major neurological symptoms included an altered level of consciousness (72%), vomiting (60%), and headache (48%). The onset of neurological symptoms to signs of brain herniation ranged from 0 days to 9 days. Nineteen (76%) patients had a seizure 24—48 hours prior to showing signs of fulminant cerebral edema, and 12 (48%) patients developed status epilepticus. Sixteen patients died, and no survivors returned to baseline. Risk factors for seizures and status epilepticus were compared between the fulminant cerebral edema group ($n = 25$, 19 seizures, including 12 status epilepticus) and control group (nonfulminant cerebral edema) ($n = 1013$, 444 seizures, including 141 status epilepticus; $p = 0.001$ for seizures and $p < 0.001$ for status epilepticus).

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Conclusion: Our findings indicate that preceding seizures and status epilepticus are significant risk factors for fulminant cerebral edema in children with acute encephalitis.

1. Introduction

Acute encephalitis most commonly occurs in children and young adults. It is characterized clinically by fever, headache, altered mental status, neurological deficits, and seizures. The prognosis of acute encephalitis in children is usually excellent; however, acute pediatric encephalitis with fulminant cerebral edema can rapidly become fatal or result in devastating neurological and cognitive sequelae. Although previous studies have reported the predictive factors of neurological outcomes in children with encephalitis,[1–6] little information is available in the literature about the incidence, clinical presentations, and outcomes of fulminant cerebral edema in children with acute encephalitis. The identification and appropriate management of pediatric encephalitis with cerebral edema often occurs in a critical care setting, and it is vital to improve the outcomes of this group of patients.[7–10] The aim of this study was to investigate fulminant cerebral edema in acute pediatric encephalitis in a series of children.

2. Methods

This retrospective study was conducted at the Department of Pediatrics, Chang Gung Children's Hospital, Taoyuan, Taiwan. All cases coded with the discharge diagnosis of acute encephalitis between January 2000 and December 2010 were reviewed.

Acute encephalitis is defined as patients diagnosed with encephalopathy plus at least two of the following criteria: (1) fever $> 38^{\circ}C$; (2) pleocytosis > 5 white blood cells/μL and/or increased protein content > 40 mg/dL in cerebrospinal fluid; (3) diffuse or focal slow activity, or epileptiform discharge on electroencephalography; and (4) abnormal neuroimaging results.[3,11,12] Fulminant cerebral edema is defined as: (1) rapidly progressive elevated intracranial pressure and neurological deterioration such as a worsening consciousness level (Glasgow coma scale < 8) and signs of brainstem dysfunction (i.e., myoclonic jerks, cranial nerve involvement, respiratory distress and shock); and (2) abnormal results of impending cerebral herniation or herniation with brainstem compression in neuroimaging including computed tomography and magnetic resonance imaging.[13–16]

All of the children were previously healthy. The exclusion criteria were age older than 18 years, purulent meningitis, electrolyte imbalance or hypoglycemia, a history of epilepsy or febrile seizures, progressive neurological disorder, and a prior neurological insult. To identify the etiology of encephalitis, serologic studies for different viruses including influenza A and B, herpes simplex virus, Epstein–Barr virus, human herpesvirus-6, *Mycoplasma pneumoniae*, and adenovirus, and polymerase chain reactions (PCRs) for herpes simplex virus in the cerebrospinal fluid were performed. In addition, viral cultures of cerebrospinal fluid, throat, and rectal swabs were also performed. The Institutional Review Board for Human Research of Chang Gung Memorial Hospital approved this study.

Information was collected including age at onset, sex, clinical symptoms, laboratory data, electroencephalography and neuroimaging findings, management, the duration of hospitalization, and the outcome. Status epilepticus and refractory status epilepticus were defined as in our previous reports.[3,11,12] Initial electroencephalograms were categorized as negative findings, focal/diffuse slow wave, or focal, multifocal, or generalized epileptiform discharges. Neuroimaging was done on admission and when there were focal neurological signs, focal seizures, and a deteriorating or severe clinical course. Outcome assessments including mortality, vegetative status, and neurological sequence were determined on discharge.

2.1. Statistical analysis

Descriptive statistical analysis of clinical and laboratory variables obtained on admission was performed. These variables included sex, age, clinical manifestations, presence of status epilepticus, cerebrospinal fluid findings, neuroimaging studies, management, and outcomes. The Chi-square test was used to compare the risk factors between the fulminant cerebral edema and control groups.

3. Results

3.1. Demographic data

During the study period, 1138 patients were discharged with the diagnosis of acute encephalitis (Figure 1). We excluded 100 patients with underlying neurological diseases, and enrolled the remaining 1038 previously healthy patients diagnosed with acute encephalitis. A total of 298 patients diagnosed with acute encephalitis were admitted to our pediatric intensive care unit. Of these patients, 25 (10 girls and 15 boys) had fulminant cerebral edema (2.4%, 25/1038). The age at onset of acute encephalitis ranged from 5 months to 16 years and 8 months [mean $\pm$ standard deviation (SD), 6.61 $\pm$ 4.24 years]. Eight (32%) patients were younger than 4 years, 12 (48%) patients were 5–8 years old, two (8%) were 9–12 years old, and three (12%) patients were older than 13 years. Most of the

patients ($n = 20$, 80%) had fulminant cerebral edema before they were 8 years old.

3.2. Clinical profile

All (25/25, 100%) of the children had a febrile prodrome, and the most common presenting neurological symptoms were an altered level of consciousness in 18 (72%) patients, vomiting in 15 (60%), patients headache in 12 (48%) patients, and behavioral disturbances in four (16%) patients. The duration from onset of neurological symptoms to signs of brain herniation ranged from 0 days to 9 days (mean $\pm$ SD, 2.7 $\pm$ 2.5 days). Nineteen (76%) of the 25 patients had a seizure 24–48 hours prior to showing signs of fulminant cerebral edema. Twelve (48%) patients developed status epilepticus, including five with refractory status epilepticus. Four patients received placement of extraventricular drainage and intracranial pressure monitors. Two patients with a normal pressure initially had refractory status epilepticus that later developed into profound cerebral edema. In addition, respiratory, gastrointestinal, or both symptoms were found in eight (32%) patient, four (16%) patient, and one (4%) patient, respectively. The demographic and clinical data of the 25 acute pediatric encephalitis patients with fulminant cerebral edema are summarized in Table 1.

The risk factors for seizures and status epilepticus were compared between the fulminant cerebral edema group ($n = 25$, 19 seizures, including 12 status epilepticus) and control group (nonfulminant cerebral edema) ($n = 1013$, 444 seizures, including 141 status epilepticus; $p = 0.001$ for seizures and $p < 0.001$ for status epilepticus).

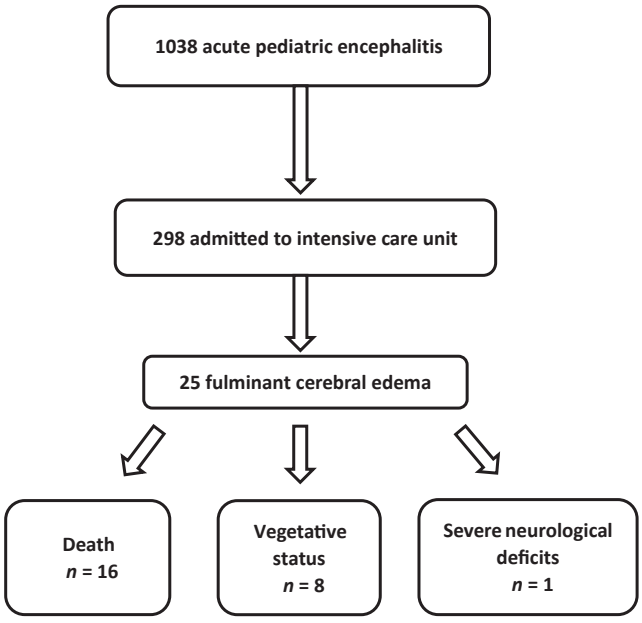

Figure 1 During the study period, 1038 patients were discharged with the diagnosis of acute encephalitis. Of these patients, 25 (10 girls and 15 boys) had fulminant cerebral edema (2.4%, 25/1038). Seizures ($p = 0.001$) and status epilepticus ($p < 0.001$) were significant risk factors for fulminant cerebral edema in the children with acute encephalitis.

Table 1 Demographic and clinical data of fulminant cerebral edema in the 25 patients with acute pediatric encephalitis.

Demographic data	*N*	%
Sex (M/F)	15/10	60/40
Age (y)		
<4	8	32
5–8	12	48
9–12	2	8
>13	3	12
Clinical manifestation		
Fever	25	100
Altered consciousness	18	72
Vomiting	15	60
Headache	12	48
Behavioral disturbances	4	16
Seizure	19	76
Status epilepticus	12	48
Refractory status epilepticus	5	20
Etiology		
Influenza A/B PCR	2/2	8/8
Mycoplasma/EBV/HSV IgM	5/2/1	20/8/4
CSF finding		
WBC (cells/μL)	0–150	
Sugar (mg/dL)	33–156	
Total protein (mg/dL)	16.6–220.4	
Brain CT		
Diffuse brain swelling	17	68
Uncal herniation	8	32
Treatment		
Hyperosmolar therapy	25	100
Hyperventilation	25	100
EVD/ICP monitors	4	16
IVIG/steroids/combined IVIG & steroids		
Outcome		
Neurological sequelae	1	4
Vegetative status	8	32
Died	16	64

CSF = cerebrospinal fluid; CT = computed tomography; EBV = Epstein-Barr virus; EVD/ICP = extraventricular drains/intracranial pressure; HSV = herpes simplex virus; IgM = immunoglobulin M; IVIG = intravenous immunoglobulin; M/F = male/female; PCR = polymerase chain reaction; WBC = white blood cell.

3.3. Etiology and cerebrospinal fluid studies

All patients underwent a thorough investigation during their hospitalization, including serologic tests for viruses, PCR of the cerebrospinal fluid for herpes simplex virus DNA ($n = 6$), PCR of throat swabs for influenza A and B ($n = 10$) and virus cultures ($n = 19$), cerebrospinal fluid ($n = 15$), and rectal ($n = 19$) specimens. Most children underwent serologic tests for herpes simplex virus ($n = 19$), Epstein–Barr virus ($n = 18$), influenza A and B ($n = 17$), *M. pneumoniae* ($n = 16$), adenovirus ($n = 14$), and human herpesvirus-6 ($n = 6$). The results of tests in the cerebrospinal fluid and blood were all negative for bacteria. Positive results for serologic tests or/and virus cultures/PCR

were noted in 12 patients, however no organism was identified in the other cases. Positive throat PCR results for influenza A and B were noted in two patients, respectively. Positive immunoglobulin M results of the serologic tests revealed five (20%) children with *M. pneumoniae*, two (8%) children with Epstein—Barr virus, and one (4%) child with herpes simplex virus. Viral cultures were identified in four (16%) throat specimens and one (4%) rectal specimen, but not (0%) in the cerebrospinal fluid.

Cerebrospinal fluid studies were conducted in 18 patients, in whom the white blood cell count ranged from 0 cells/μL to 150 cells/μL (median, 7 cells/μL) with a predominance of monocytes (60—100%). The glucose level in the cerebrospinal fluid ranged from 33 to 156 mg/dL (median, 44 mg/dL), and the total protein level ranged from 16.6 mg/dL to 220.4 mg/dL (median, 77 mg/dL). Ten (56%) of these patients received a lumbar puncture more than 24 hours prior to the occurrence of uncal herniation, four (22%) of them within 24 hours and another four (22%) after the event.

3.4. Electroencephalography and neuroimaging findings

Eleven patients received electroencephalography examinations prior to brain herniation, and 11 patients received electroencephalography examinations after brain herniation. In the before-brain herniation group, the initial electroencephalography result was negative in one patient, with focal/diffuse cortical dysfunction in four patients, focal epileptiform discharge in two patients, generalized epileptiform discharge in three patients, and multifocal epileptiform discharge in one patient. In the after-herniation group, all electroencephalography results showed electrocortical silence.

All patients underwent brain computed tomography on admission. Seventeen of the 25 (68%) patients had a nonspecific increased leptomeningeal enhancement or brain swelling, but all had evidence of brain herniation in follow-up imaging (Figure 2). The other eight patients had evidence of brain herniation in the initial computed tomography scan.

3.5. Treatment, hospital course, and outcome

With respect to management, 19 patients received acyclovir and 12 patients received oseltamivir therapy. In addition to antiviral treatment, all (100%) patients received hyperosmolar therapy prior to showing signs of fulminant cerebral edema. After signs of fulminant cerebral edema had occurred, all (100%) patients received hyperventilation for 24 hours, and four (16%) patients received placement of extraventricular drains/intracranial pressure monitors. In addition, 10 (40%) patients received intravenous immunoglobulin, two (8%) patients received intravenous high-dose methylprednisolone, and three (12%) patients received a combination of intravenous immunoglobulin and high-dose methylprednisolone as immune modulating therapy. The duration to onset of signs of brain herniation after admission to the pediatric intensive care unit ranged from 0 days to 8 days (mean ± SD, 1.48 ± 1.89 days). Nineteen (76%) patients developed brain herniation 24 hours after admission to the pediatric intensive care unit.

The duration of hospitalization ranged from 2 days to 113 days (mean ± SD, 28.71 ± 29.48 days). With regard to the outcomes of the 25 children, 16 (64%) died because of severely increased intracranial pressure with profound shock or discharge against medical advice, eight (32%) developed a vegetative status, and one (4%) developed a severe neurological sequelae. The laboratory data, neuroimaging, treatment, and outcomes of the 25 children are listed in Table 1.

4. Discussion

Acute pediatric encephalitis can cause medically refractory intracranial hypertension and brain herniation. In such patients, death is common. There is a paucity of data on the incidence and outcomes of fulminant cerebral edema in children with acute encephalitis. In the California Encephalitis Project from 1998 to 2005, 47 (3%) of 1570 cases of encephalitis presented with the rapid evolution to fulminant cerebral edema, and 34 (72.3%) patients died within 7 days after hospitalization.[17] In our study, 25 (2.4%) of 1038 children with encephalitis presented with fulminant cerebral edema, 16 (64%) of whom died because of severely increased intracranial pressure with profound shock or were discharged against medical advice, eight (32%) developed a vegetative status, and one (4%) developed a severe neurological sequelae. Therefore, although fulminating cerebral edema in acute pediatric encephalitis is very unusual, potentially life-threatening complications are possible.

The early recognition of fulminant cerebral edema is essential in view of the propensity to a sudden and fatal outcome. The most common symptoms that are generally considered indicative of raised intracranial pressure include headache, vomiting, and an altered level of consciousness.[13—16] Therefore, close monitoring of these symptoms and signs in children with acute encephalitis is very important. In addition, seizures and status epilepticus can also lead to an elevated intracranial pressure in children.[18] In this study, two patients initially had refractory status epilepticus with a normal intracranial pressure. Both of these patients subsequently developed profound cerebral edema. Therefore, the presence of seizures and status epilepticus may also be important risk factors in these patients. Signs of brainstem involvement may be another clue for fulminant cerebral edema and brain herniation in children with encephalitis. When the brainstem is involved as a consequence of herniation, features of extension to pain, breathing abnormalities, a myriad of eye signs such as pupillary dilatation and impaired upgaze, and decerebrate and decorticate posturing have been reported.[13—16] In a literature review of decompressive craniectomy for the treatment of encephalitis-related brain edema, the authors concluded that brainstem compression is probably an important sign that the procedure should be performed.[19]

In the current study, 80% of the patients had fulminant cerebral edema before they were 8 years old. The most common presenting neurological symptoms were an altered level of consciousness (72%), vomiting (60%), and headache

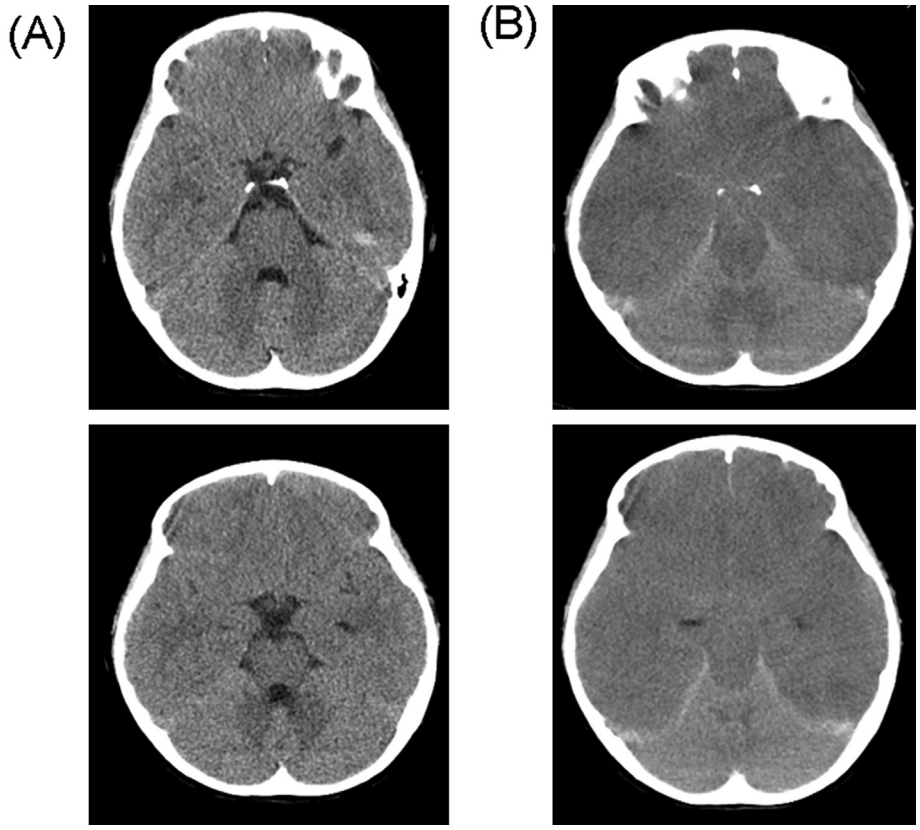

Figure 2 (A) Brain computed tomography of a 7-year-old girl with acute encephalitis showed a nonspecific finding initially, (B) but evidence of uncal herniation in follow-up imaging the next day.

(48%). The mean duration from the onset of neurological symptoms to signs of brain herniation was $<$ 3 days (mean $\pm$ SD, 2.7 $\pm$ 2.5 days). It is difficult to predict uncal herniation early because the symptoms and signs of increasing intracranial pressure in acute encephalitis are nonspecific. However, 76% of the patients had a seizure ($p = 0.001$) 24—48 hours prior to showing signs of fulminant cerebral edema, and 48% of the patients developed status epilepticus ($p < 0.001$). This suggests that the presence of seizures or status epilepticus, and onset of neurological symptoms within 3 days may be important clues for the development of fulminant cerebral edema in children with acute encephalitis. In addition, this may be the optimal period in which to perform brain imaging to evaluate brain edema and to initiate interventions such as more aggressive seizure control, surgical intervention, or anti-inflammation therapy based on the underlying etiology.

Some physicians advocate aggressive nonsurgical intracranial pressure management in patients with fulminant cerebral edema resulting in rapid neurological deterioration, including hyperosmolar therapy, hyperventilation, therapeutic hypothermia, and steroids. Surgical interventions may be necessary in some cases despite aggressive nonsurgical management, including intracranial pressure monitoring, external ventricular drainage, and decompressive craniectomy.[14—16] A literature review of 43 patients who underwent decompressive craniectomy for encephalitis-related brain edema reported a mortality rate of 4% and a rate of good recovery of 81%.[19] Although this result is encouraging, the small number of patients limits the conclusions that can be drawn. In our study, in addition to antiviral treatment, all patients received hyperosmolar therapy prior to showing signs of fulminant cerebral edema. After signs of fulminant cerebral edema had developed, all of the patients received hyperventilation for 24 hours, and four patients received placement of extraventricular drains/intracranial pressure monitors. None of the patients received decompressive craniectomy. Sixteen patients died and none returned to baseline. We recommend that if medical management of elevated intracranial pressure in patients with acute pediatric encephalitis and fulminant cerebral edema fails, decompressive craniectomy may be considered as an option.

5. Conclusion

Although fulminant cerebral edema in children with acute encephalitis is relatively uncommon, the severity and rapid evolution of the disease highlight the importance of understanding why certain children progress along this pathway. Our findings suggest that preceding seizures and status epilepticus are significant risk factors for fulminant cerebral edema in children with acute encephalitis. Early recognition of the risk factors of this complication is essential in view of the propensity to sudden and fatal outcome.

Conflicts of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

Acknowledgments

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